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# Biomarkers for major depression and its delineation from neurodegenerative disorders

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ABSTRACT

Major depressive disorders (MDD) are among the most debilitating diseases worldwide and occur with a high prevalence in elderly individuals. Neurodegenerative diseases (in particular Alzheimer's disease, AD) do also show a strong age-dependent increase in incidence and prevalence among the elderly population. A high number of geriatric patients with MDD show cognitive deficits and a very high proportion of AD patients present co-morbid MDD, which poses difficult diagnostic and prognostic questions. Especially in prodromal and in very early stages of AD, it is almost impossible to differentiate between pure MDD and MDD with underlying AD.

Here, we give a comprehensive review of the literature on the current state of candidate biomarkers for MDD ("positive MDD markers") and briefly refer to established and validated diagnostic AD biomarkers in order to rule out underlying AD pathophysiology in elderly MDD subjects with cognitive impairments ("negative MDD biomarkers"). In summary, to date there is no evidence for positive diagnostic MDD biomarkers and the only way to delineate MDD from AD is to use "negative MDD" biomarkers.

Because of this highly unsatisfactory current state of MDD biomarker research, we propose a research strategy targeting to detect and validate positive MDD biomarkers, which is based on a complex (genetic, molecular and neurophysiological) biological model that incorporates current state of the art knowledge on the pathobiology of MDD. This model delineates common pathways and the intersection between AD and MDD. Applying these concepts to MDD gives hope that positive MDD biomarkers can be successfully identified in the near future.



**Contents**



*Abbreviations:* ACTH, adrenocorticotropes hormone; AD, Alzheimer's disease; APLP2, amyloid precursor-like protein 2; ACE, angiotensin-converting enzyme; ACC, anterior cingulate cortex; AVP, arginine-vasopressin; ASL, arterial spin labeling; DA, axial diffusion; BOLD, blood oxygen level dependent; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; CBV, cerebral blood volume; CSF, cerebrospinal fluid; CRH, corticotrophin-releasing hormone; CRHR2, corticotropin releasing hormone receptor 2; Cr, creatine; DMN, default mode network; DG, dentate gyrus; DEX, dexamethasone; DTI, diffusion tensor imaging; DLPFC, dorsolateral prefrontal cortex; FDG, fluordeoxyglucose; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; MRI, magnetic resonance imaging; MDD, major depressive disorder; MD, mean diffusion; MCI, mild cognitive impairment; NAA, N-acetyl-aspartate; OFC, orbitofrontal cortex; OMPFC, orbitomedial prefrontal cortex; PVN, paraventricular nucleus; pCREB, phosphorylated cyclic adenosine monophosphate response element-binding protein; p-tau, phosphorylated tau; PET, positron emission tomography; PFC, prefrontal cortex; pgACC, pregenual anterior cingulate cortex; DR, radial diffusion; rACC, rostral anterior cingulum; 5-HTTLPR, serotonin transporter promoter; 5-HT, serotonin; sAPP, soluble amyloid precursor protein; SGPFC, subgenual prefrontal cortex; sgACC, supragenual ACC; vlPFC, ventro-lateral prefrontal cortex.

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## 1. Introduction

### 1.1. Intersection of dementia and depression in elderly population – a rationale for biomarker use

Major depression is among the most debilitating diseases worldwide with highest reductions in disability adjusted years of life among all human diseases (Falagas et al., 2007). Lifetime prevalence of major depressive disorder (MDD) is up to 20% (Williams et al., 2007). In the elderly, depression is the second most common psychiatric disorder (Panza et al., 2010).

Both, dementia and depression represent clinical syndromes with a large variety of underlying etiologies. Incidence and prevalence rates of both syndromes increase with advanced age and they appear to interact with each other: on the one hand depression leads to objective cognitive impairments, on the other hand cognitively impaired and demented individuals are at substantially increased risk to develop depression. Depression has a more than threefold higher prevalence in demented subjects compared with cognitively intact individuals of same age (Lyketsos et al., 2000; Lyketsos and Olin, 2002). MDD has a prevalence of up to 25% in AD patients, which more than doubles if minor depression is counted as well (Olin et al., 2002; Usman et al., 2010; Zubenko et al., 2003) and an even higher prevalence in vascular dementia (Ballard et al., 1996, 2000; Park et al., 2007). It is of interest that depression and anxiety symptoms have been associated with an accelerated cognitive decline in AD (Starkstein et al., 2008).

While these findings suggest a strong association between dementia and depression, data on depression as a possible risk factor for dementia, are less clear. A number of case–control and cohort studies suggest that depression might increase the risk to develop dementia (Andersen et al., 2005; Kokmen, 1991; Speck et al., 1995; Tsolaki et al., 1997). However, these results could not be confirmed by other studies (Lindsay et al., 2002). The picture changes a lot when only late-onset depression is considered: there is substantial evidence in support for the hypothesis that late-onset depression may be an early or prodromal sign of a dementia disorder or another neurodegenerative disease, especially when paired with transient cognitive impairments: indeed, elderly subjects with recent (late-onset) depression show significantly elevated incidence of subsequent AD (Alexopoulos et al., 1993a,b; Jorm, 2001).

In summary, existing evidence points to a high co-morbidity of MDD and AD with late-onset depression being an early sign of prodromal AD. The neurobiological basis of MDD in AD may be the early affection of subcortical areas such as the locus coeruleus and raphe nuclei which are frequently observed in AD (Förstl et al., 1992; Rüb et al., 2000; Zubenko, 1992). These nuclei are key elements of serotonergic and norpepinephrine neurotransmission in the brain. Deficits in serotonergic and norepinepephrine signalling are generally considered as the basis for many depressive symptoms and are targeted by current antidepressant therapy.

Genetic factors that have been described to be associated with an increased risk of MDD and AD comprise polymorphisms in genes encoding for inflammatory cytokines (McCulley et al., 2004) and for BDNF.

In addition to a shared neuropathology of subcortical structures relevant to depression, psychological factors may also play a role in the high incidence of MDD in AD: it is plausible to assume that individuals who realize their progressive cognitive and functional decline may react with depressive symptoms. However, some studies did not find an association between the level of insight and depressive symptoms, which points to biological rather than to psychological factors being the major driving cause for increased MDD incidence in dementia (Salmon et al., 2006).

A major diagnostic and prognostic problem is posed by the high co-morbidity of dementia and depression and by the fact that dementia disorders (AD in particular) have a relatively long preclinical prodromal stage without dementia symptoms. Two important questions relevant to clinical practice arise from this constellation:

1. Which elderly patients with (late-onset) MDD may already suffer from prodromal AD and will develop clinical dementia within the next years?
2. Which tools are useful to correctly classify MDD patients and AD patients with co-morbid MDD during preclinical AD stages?

As shown in Table 1, cognitive symptoms in MDD and AD do overlap in such a high degree that they are not useful to clearly differentiate between “pure” MDD and AD with comorbid MDD on an individual level in most cases (Robbins et al., 1996).

While the differential diagnosis between full-blown, manifest dementia and MDD is generally not difficult to accomplish when the severity of functional disability reaches levels unique for moderate and severe dementia (e.g. disorientation in space, time, and situation, apraxia) the picture changes substantially in patients during very early or prodromal stages of AD with isolated and relatively mild cognitive symptoms being compatible with both MDD associated cognitive deficits and cognitive deficits due to very early stages of AD or mild cognitive impairment (MCI).

To our knowledge, to date, systematic research has not been done to quantify cases of geriatric patients with MDD being